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$BF_3.Et_2O$ catalyzed synthesis and antioxidant evaluation of benzyl/arylphosphonates

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ABSTRACT

*A series of novel benzyl/arylphosphonates were synthesized by the $BF_3.Et_2O$ catalyzed Michaelis-Arbuzov reaction where by the reaction of 3-trifluorobenzylbromide/5-bromonicotinic acid with various trialkyl phosphites in the N_2 atmosphere. All the synthesized compounds were characterized by their spectral analysis. The title compounds were screened for their anti-oxidant activity DPPH and Superoxide radical scavenging activities. The compounds **3d**, **3i** and**3j** were exhibited the good consequences.*

K**ey words**: Benzyl/Arylphosphonates, 3-trifluorobenzylbromide/5-bromonicotinic acid, Anti-oxidant activity.

INTRODUCTION

P-C bond is playing an important role in preserving so many syndromes and in the synthesis of numerous anticancer [1], antiviral [2], antimicrobial [3], anti-diabetic [4] and antioxidant agents. Detailed focus on the mechanism of antioxidant action of organophosphorus compounds and their structure-activity relationship, Phosphite and phosphonatesare acting as both primary and secondary antioxidants [5-6]. 2-Substituted-thiadiazaphosphol-2-ones exhibited promising antioxidant properties [7]. In addition that various phosphorylated nucleosides and organophosphorus compounds showed good antioxidant, antimicrobial and anticancer activities [8-10]. Another series of diazaphospholoiminophosphorane derivatives containing zidovudine displayed significant antioxidant properties [11]. Various heterocyclic are also developed in Organophosphorus chemistry to develop bio-potent molecules [12]. Previously various pyrimidines and tetrahydropyrimidines were developed and stated the as good antiviral and antioxidant agents in our laboratory [13-14].

Although several synthetic methods are described for the preparation of such compounds, one of the most versatile is the Michaelis-Arbuzov reaction. Unfortunately, it has some drawbacks when use classical conditions such as length of reaction time, high temperature and removal of the trialkyl phosphite used in a large excess. These drastic conditions may be responsible for side reactions, low yields and limits the application of such reactions to sensitive substrates. Recently, researchers are focused on Lewis acids. In this connection we selected $BF_3.Et_2O$ as efficient catalyst for nucleophilic substitution to synthesis the heteroarylphosphonate derivatives *via* Michaelis-Arbuzov reaction. All the compounds were screened for their antioxidant activity.

MATERIALS AND METHODS

Experimental

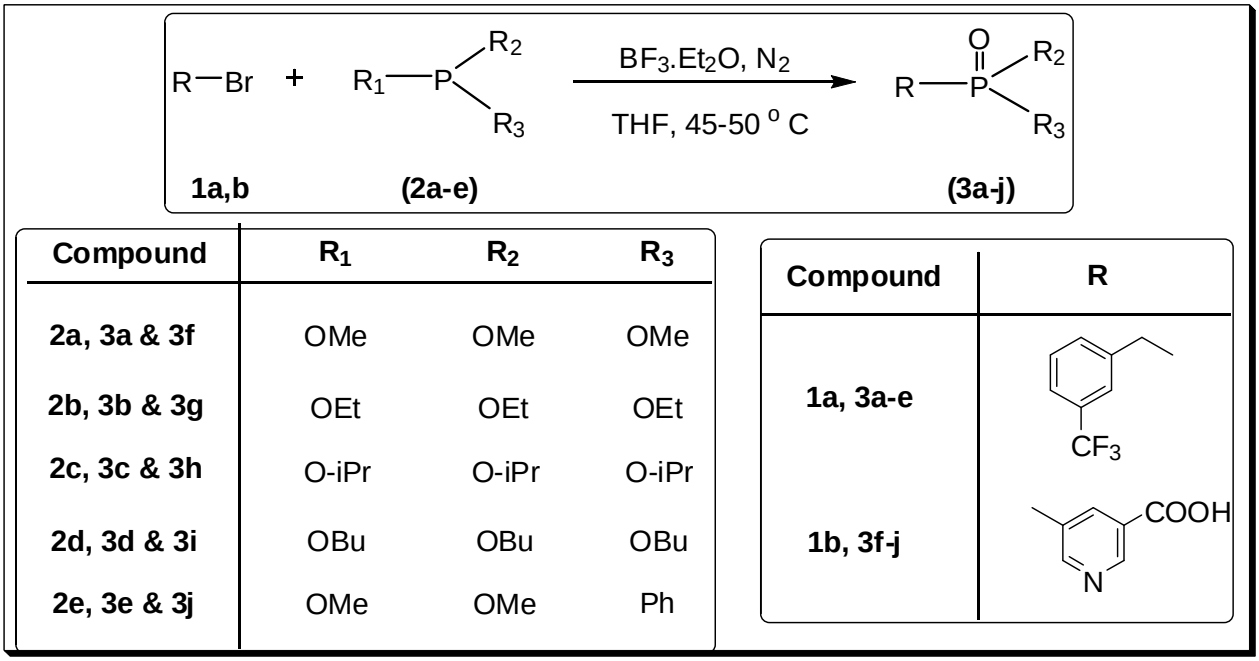
Chemistry

Chemicals were procured from Sigma–Aldrich and Merck were used as such without further purification. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods [15]. Melting points (m p) were determined using a calibrated thermometer by Guna Digital Melting Point apparatus. They expressed in degrees centigrade (^oC) and are uncorrected. Infrared spectra (IR) were obtained on a

Perkin-Elmer Model 281-B spectrophotometer. Samples were analyzed as potassium bromide (KBr) disks. Absorptions were reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded as solutions in DMSO-$d_6$on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^1H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P NMR. The ^1H and ^{13}C chemical shifts were expressed in parts per million (ppm) with reference to tetramethylsilane (TMS) and ^{31}P chemical shifts to 85% H_3PO_4. LCMS mass spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer.

Synthetic protocol for Dimethyl 3-(trifluoromethyl)benzylphosphonate(3a)

Triflouromethylbenzylbromide(**1a**) (0.001 mol) in dry THF (10 mL) was added to trimethylphospite (**2a**) under N_2 atmosphere in the presence of $BF_3.Et_2O$ (0.0002 mol) and the reaction mixture was refluxed for 3 h at 45-50 ^oC. The progress of the reaction was monitored by TLC using ethyl acetate: hexane (1:1). After completion of the reaction, catalyst was removed by filtration and the filtrate was concentrated in vacuum to afford the crude product. It was purified by silica gel column chromatography eluting with ethyl acetate: hexane (1:1) mixture to afford the title compound, Dimethyl 3-(trifluoromethyl)benzylphosphonate(**3a**). The same experimental procedure was adopted for the preparation of the remaining title compounds **3b-j (Scheme 1)**.



Compound	R_1	R_2	R_3
2a, 3a & 3f	OMe	OMe	OMe
2b, 3b & 3g	OEt	OEt	OEt
2c, 3c & 3h	O-iPr	O-iPr	O-iPr
2d, 3d & 3i	OBu	OBu	OBu
2e, 3e & 3j	OMe	OMe	Ph

Compound	R
1a, 3a-e	
1b, 3f-j	

Scheme 1:

Dimethyl 3-(trifluoromethyl)benzylphosphonate (3a):

Yield: 89 %, mp: 136-138 °C. IR (KBr) (ν_{max} cm^{-1}): 1245 (P=O), 752 (P-$C_{aliphatic}$). ^1H NMR (400 MHz, $CDCl_3$) δ: 3.24 (2H, d, J = 24.2 Hz, P-CH_2), 3.66 (3H, d, J = 10.2 Hz, P-OCH_3), 3.70 (3H, d, J = 10.2 Hz, P-OCH_3), 7.23-7.49 (4H, m, Ar-H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 49.0 (d, J = 152.4 Hz, P-CH_2), 53.0 (d, J = 8.0 Hz, P-OCH_3), 53.3 (d, J = 7.8 Hz, P-OCH_3), 122.3 (C-4), 123.8 (Ar-CF_3), 127.0 (C-2), 128.8 (C-5), 130.2 (C-3), 133.3 (C-1), 135.8 (C-6).^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 21.58. EI-MS (m/z, %): 269 (M+1, 100), 268 (M+•, 20). Anal.Calcd for $C_{10}H1_2F_3O_3P$: C, 44.79; H, 4.51. Found: C, 44.72; H, 4.48.

Diethyl 3-(trifluoromethyl)benzylphosphonate (3b):

Yield: 84 %, mp: 148-150 °C. IR (KBr) (ν_{max} cm^{-1}): 1252(P=O), 737(P-$C_{aliphatic}$).^1H NMR (400 MHz, $CDCl_3$) δ: 1.14 (3H, t, J = 7.4 Hz, P-$OCH_2C\underline{H}_3$), 1.21 (3H, t, J = 7.2 Hz, P-$OCH_2C\underline{H}_3$), 3.26 (2H, d, J = 24.4 Hz, P-CH_2), 3.61-3.72 (1H, m, P-$OC\underline{H}_2CH_3$), 3.81-3.95 (1H, m, P-$OC\underline{H}_2CH_3$), 4.01-4.14 (2H, m, P-$OC\underline{H}_2CH_3$), 7.02-7.56 (4H, m, Ar-H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 16.2 (d, J = 5.8 Hz, P-$OCH_2\underline{C}H_3$), 16.4 (d, J = 5.8 Hz, P-$OCH_2\underline{C}H_3$),58.7 (d, J = 152.2 Hz, P-CH_2), 63.2 (d, J = 7.0 Hz, P-$O\underline{C}H_2CH_3$), 64.2 (d, J = 7.2 Hz, P-$O\underline{C}H_2CH_3$), 121.3 (C-4), 122.2 (Ar-CF_3), 125.5 (C-2), 129.9 (C-5), 133.6 (C-3), 135.5 (C-1), 139.2 (C-6). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 20.60. EI-MS (m/z, %): 297 (M+1, 100), 296 ($M^{+\bullet}$, 20). Anal. Calcd for $C_{12}H_{16}F_3O_3P$: C, 48.66; H, 5.44. Found: C, 48.61; H, 5.40.

Diisopropyl 3-(trifluoromethyl)benzylphosphonate (3c):

Yield: 92 %, mp: 171-173 °C. IR (KBr) (ν_{max} cm^{-1}): 1228(P=O), 743(P-$C_{aliphatic}$).^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (12H, d, J = 6.6 Hz, -CH_3), 3.38 (2H, d, J = 24.0 Hz, P-CH_2), 4.47-4.81 (2H, m, -OCH), 7.25-7.94 (4H, m, Ar-H).

^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 21.5 (d, *J* = 6.2 Hz, 4 X -CH_3), 46.2 (d, *J* = 152.8 Hz, P-CH_2), 72.8 (d, *J* =7.4 Hz, 2 X P-OCH), 122.5 (C-4), 124.8 (Ar-CF_3), 127.7 (C-2), 128.4 (C-5), 130.2 (C-3), 133.3 (C-1), 135.8 (C-6). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 22.78. EI-MS (m/z, %): 325 (M+1, 100), 324 ($M^{+\bullet}$, 20). Anal. Calcd for $C_{14}H_{20}F_3O_3P$: C, 51.85; H, 6.22. Found: C, 51.81; H, 6.17.

Dibutyl 3-(trifluoromethyl)benzylphosphonate (3d):
Yield: 85 %, mp: 182-184 °C. IR (KBr) (ν_{max} cm^{-1}): 1238(P=O), 751(P-$C_{aliphatic}$).^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (3H, t, *J* = 6.4 Hz, P-$OCH_2C\underline{H}_3$), 1.05 (3H, t, *J* = 6.4 Hz, P-$OCH_2C\underline{H}_3$), 1.42-1.53 (4H, m, -$C\underline{H}_2CH_3$), 1.65-1.74 (4H, m, -$C\underline{H}_2CH_2$), 3.37 (2H, d, *J* = 24.8 Hz, P-CH_2), 4.01-4.17 (2H, m, P-$OC\underline{H}_2CH_2$), 7.16-8.84 (4H, m, Ar-H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 13.9 (2 X CH_3), 18.0 (2 X -CH_2),31.9 (2 X -CH_2), 46.0 (d, *J* = 152.2 Hz, P-CH_2), 66.0 (d, *J* = 10.8 Hz, 2 X P-$O\underline{C}H_2$), 122.0 (C-4), 125.4 (Ar-CF_3), 128.0 (C-2), 128.5 (C-5), 129.9 (C-3), 133.8 (C-1), 136.8 (C-6). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 24.57. EI-MS (m/z, %): 352 (M+1, 100), 351 ($M^{+\bullet}$, 20). Anal. Calcd for $C_{16}H_{24}F_3O_3P$: C, 54.54; H, 6.87. Found: C, 54.49; H, 6.82.

Methyl phenyl(3-(trifluoromethyl)benzyl)phosphinate (3e):
Yield: 93 %, mp: 179-181 °C. IR (KBr) (ν_{max} cm^{-1}): 1218(P=O), 764(P-$C_{aliphatic}$).^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.41 (2H, d, *J* = 24.6 Hz, P-CH_2), 3.65 (3H, d, *J* = 10.2 Hz, P-OCH_3), 7.12-8.99 (9H, m, Ar-H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 44.2 (d, *J* = 152.6 Hz, P-CH_2), 53.0 (d, *J* = 8.0 Hz, P-OCH_3), 120.4 (C-2' & C-6'), 121.4 (C-4'), 125.8 (Ar-CF_3), 127.6 (C-2), 129.5 (C-3), 130.4 (C-3' & C-5'), 132.9 (C-1), 150.2 (C-1'), 128.8 (C-5), 122.2 (C-4), 135.4 (C-6). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 22.89. EI-MS (m/z, %): 315 (M+1, 100), 314 ($M^{+\bullet}$, 20). Anal. Calcd for $C_{15}H_{14}F_3O_2P$: C, 57.33; H, 4.49. Found: C, 57.28; H, 4.45.

5-(dimethoxyphosphoryl)nicotinic acid (3f):
Yield: 87 %, mp: 157-159 °C. IR (KBr) (ν_{max} cm^{-1}): 1716 (C=O), 1246(P=O), 738(P-$C_{aliphatic}$).^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.72 (3H, d, *J* = 7.2 Hz, P-OCH_3), 3.81 (3H, d, *J* = 7.6 Hz, P-OCH_3), 7.30-7.88 (3H, m, Ar-H), 11.01 (1H, s, OH). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 52.8 (d, *J* = 5.0 Hz, P-OCH_3), 53.6 (d, *J* = 5.0 Hz, P-OCH_3), 128.4 (C-3), 130.2 (C-1), 138.1 (C-2), 153.3 (C-5), 154.6 (C-4), 166.6 (C=O). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 22.84. EI-MS (m/z, %): 232 (M+1, 100), 230 ($M^{+\bullet}$, 20). Anal. Calcd for $C_8H_{10}NO_5P$: C, 41.57; H, 4.36; N, 6.06. Found: C, 41.52; H, 4.31; N, 6.02.

5-(diethoxyphosphoryl)nicotinic acid (3g):
Yield: 90 %, mp: 165-167 °C. IR (KBr) (ν_{max} cm^{-1}): 1718 (C=O), 1218(P=O), 756(P-$C_{aliphatic}$).^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (3H, t, *J* = 7.0 Hz, P-$OCH_2C\underline{H}_3$), 1.19 (3H, t, *J* = 7.5 Hz, P-$OCH_2C\underline{H}_3$), 3.62-3.72 (1H, m, P-$OC\underline{H}_2CH_3$), 3.82-3.93 (1H, m, P-$OC\underline{H}_2CH_3$), 4.02-4.19 (2H, m, P-$OC\underline{H}_2CH_3$), 7.30-7.88 (3H, m, Ar-H), 11.08 (1H, s, OH). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 16.1 (d, *J* = 6.2 Hz, P-$OCH_2\underline{C}H_3$), 16.4 (d, *J* = 6.2 Hz, P-$OCH_2\underline{C}H_3$),62.6 (d, *J* = 10.0 Hz, P-$O\underline{C}H_2CH_3$), 62.7 (d, *J* = 7.5 Hz, P-$O\underline{C}H_2CH_3$), 123.6 (C-1), 127.5 (C-3), 140.1 (C-2), 155.1 (C-4), 157.3 (C-5), 164.9 (C=O). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 23.48. EI-MS (m/z, %): 260 (M+1, 100), 259 ($M^{+\bullet}$, 20). Anal. Calcd for $C_{10}H_{14}N_2O_5P$: C, 46.34; H, 5.44; N, 5.40. Found: C, 46.30; H, 5.41; N, 5.35.

5-(diisopropoxyphosphoryl)nicotinic acid (3h):
Yield: 91 %, mp: 175-177 °C. IR (KBr) (ν_{max} cm^{-1}): 1715 (C=O), 1238(P=O), 741(P-$C_{aliphatic}$).^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (12H, d, *J* = 6.8 Hz, -CH_3), 4.42-4.78 (2H, m, -OCH), 7.28-7.89 (3H, m, Ar-H), 11.07 (1H, s, OH). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 20.8 (d, *J* = 6.2 Hz, 4 X -CH_3), 72.0 (d, *J* = 7.7 Hz, 2 X P-OCH), 125.2 (C-1), 127.2 (C-3), 140.4 (C-2), 154.2 (C-4), 156.3 (C-5), 166.1 (C=O). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 22.15. EI-MS (m/z, %): 288 (M+1, 100), 287 ($M^{+\bullet}$, 20). Anal. Calcd for $C_{12}H_{18}NO_5P$: C, 50.18; H, 6.32; N, 4.88. Found: C, 50.14; H, 6.25; N, 4.82.

5-(dibutoxyphosphoryl)nicotinic acid (3i):
Yield: 92 %, mp: 193-195 °C. IR (KBr) (ν_{max} cm^{-1}): 1720 (C=O), 1226(P=O), 768(P-$C_{aliphatic}$).^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, t, *J* = 6.2 Hz, P-$OCH_2C\underline{H}_3$), 1.19 (3H, t, *J* = 6.8 Hz, P-$OCH_2C\underline{H}_3$), 1.41-1.54 (4H, m, -$C\underline{H}_2CH_3$), 1.67-1.79 (4H, m, -$C\underline{H}_2CH_2$), 4.04-4.18 (2H, m, P-$OC\underline{H}_2CH_2$), 7.88-8.98 (3H, m, Ar-H), 11.10 (1H, s, OH). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 13.7 (2 X -CH_3), 18.4 (2 X -CH_2),31.2 (2 X -CH_2), 66.6 (d, *J* = 10.2 Hz, 2 X P-$O\underline{C}H_2$), 125.5 (C-1), 127.4 (C-3), 140.7 (C-2), 155.0 (C-4), 156.3 (C-5), 166.9 (C=O). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 21.44. EI-MS (m/z, %): 316 (M+1, 100), 315 ($M^{+\bullet}$, 20). Anal. Calcd for $C_{14}H_{22}N_2O_5P$: C, 53.33; H, 7.03; N, 4.44. Found: C, 53.28; H, 7.00; N, 4.39.

5-(methoxy(phenyl)phosphoryl)nicotinic acid(3j):
Yield: 84 %, mp: 146-148 °C. IR (KBr) (ν_{max} cm^{-1}): 1710 (C=O), 1224(P=O), 751(P-$C_{aliphatic}$).^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.70 (3H, d, *J* = 7.2 Hz, P-OCH_3), 7.12-8.99 (8H, m, Ar-H), 11.24 (1H, s, OH). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 52.6 (d, *J* = 5.8 Hz, P-OCH_3), 120.7 (C-2' & 6'), 121.5 (C-4'), 128.4 (C-3), 130.7 (C-3' & 5'), 132.4 (C-1),

138.6 (C-2), 150.4 (C-1'), 153.9 (C-5), 154.8 (C-4), 167.7 (C=O). ^{31}P NMR (161.7, MHz, $CDCl_3$) δ: 22.25. EI-MS (m/z, %): 356 (M+1, 100), 355 ($M^{+\bullet}$, 20). Anal. Calcd for $C_{13}H_{12}NO_4P$: C, 56.32; H, 4.36; N, 5.05. Found: C, 56.28; H, 4.31; N, 5.01.

Antioxidant activity

Antioxidant activity of the title compounds was evaluated with two methods DPPH and Super Oxide radical scavenging activities. Scavenging capacity was measured spectrophotometrically by monitoring the decrease in absorbance at 517 nm.

DPPH radical-scavenging activity

The DPPH radical scavenging activity was measured in a reaction mixture containing 1 mM DPPH radical solution 0.1 mL, 99% ethanol 0.8 mL, and 0.1 mL of each one of the studied compounds prepared by dissolving the compound in methanol. The solution was rapidly mixed and scavenging capacity was measured spectrophotometrically by monitoring the decrease in absorbance at 517 nm.

$$\text{DPP}\dot{\text{H}}\text{ Scavenging activity (\%)} = \frac{1 - \text{Absorbance of sample at 517 nm}}{\text{Absorbance of control at 517 nm}} X100$$

Superoxide radical scavenging activity

Superoxide radicals were determined using spectrophotometric measurement of the effects of various concentrations of test compounds on the reduction of nitrobluetetrazolium (NBT), according to a previously described procedure.[17] Superoxide radicals were generated in a non-enzymatic phenazinemethosulfate/nicotinamide adenine dinucleotide (PMS/NADH) system. The non-enzymatic generation of superoxide radicals was measured in reaction mixtures containing various concentrations of test compounds, PMS (15 µM), NADH (73 µM), and NBT (50 µM) in phosphate buffer (20 mM, pH 7.4). After incubation for 5 min at ambient temperature, the color was read at 560 nm against blank samples.

$$\text{Scavenging activity (\%)} = \frac{\text{Absorbance of control} - \text{absorbance of test samples}}{\text{absorbance of control}} X100$$

Reactive oxygen species (ROS), such as superoxide anion radical ($O^{2-\cdot}$), hydroxyl adicals (OH) and peroxyl radicals ($ROO^{\cdot}$) are produced as a part of normal metabolic processes [16]. The compounds **(3a-l)** showed significant antioxidant activity by scavenging the free radicals and superoxide radicals.

The antioxidant activity evaluation with the 1,1-diphenyl-2-picryl-hydrazyl (DPPH), radical-scavenging assay was carried out [17] and the results are presented in **Table-3.**

Table-1.Antioxidant activities of the title compounds 3(a-l)

Compound	DPPH$^{\cdot}$ Scavenging (%)	Superoxide Scavenging (%)
3a	58.02±1.21	56.17±1.43
3b	62.48±1.23	59.22±1.05
3c	68.84±1.28	66.45±1.04
3d	74.13±1.01	69.93±1.76
3e	40.87±1.05	39.34±1.43
3f	47.34±1.46	45.65±1.19
3g	50.93±1.83	68.19±1.37
3h	58.68±1.22	69.79±1.38
3i	71.43±1.14	70.06±1.01
3j	77.09±1.28	74.98±1.53
3k	74.53±1.06	75.87±1.12
3l	78.71±1.06	76.67±1.19
Ascorbic acid	83.92±1.10	78.12±1.13

[a] concentration 100 µg/mL

RESULTS AND DISCUSSION

Various phosphorylated derivatives of Triflouromethyl benzylbromide (**1a**) and 5-bromonicotinic acid (**1b**) were synthesized by their nucleophilic substitution with various trivalent phosphites under N_2 atmosphere where $BF_3.Et_2O$ as a catalyst at 45-50 ^oC. After completion of the reaction, catalyst was removed by filtration and the filtrate was concentrated in vacuum to afford the crude product. It was purified by silica gel column chromatography. The pure products were characterized by IR, (^1H, ^{13}C, ^{31}P) NMR, Mass spectral data and elemental analysis.

The chemical structures of all the title compounds **3a-l** were characterized by IR, (^1H, ^{13}C, ^{31}P) NMR, mass spectral data and elemental analyses and their data are presented in experimental section. IR absorptions were observed in the regions 1710-1720, 1218-1252 and 737-768 cm^{-1} are assigned to C=O, P=O and P-C respectively for **3a-j** [18-20**].** The ^1H NMR signals of PCH_2 were appeared in high field i.e. in between δ 3.24-3.48 due to the substitution of Br with P for the compounds **3a-e**. ^{13}C NMR chemical shifts δ 44.2-58.7 of the compounds **3a-e and** δ 164.9-167.7 of **3f-j** are indicating the PCH_2 and C=O carbon signals attached to P atom. ^{31}P NMR signals of all the title compounds were observed in between δ 20.60-24.57. Mass and elemental analysis of the title compounds were correlated with the expected values.

Antioxidant activity

All the title compounds **3a-j** screened for their antioxidant activity by DPPH radical-scavenging and Superoxide radical scavenging methods. The title compounds **3a-j** showed good antioxidant activity. Especially compounds **3d**, **3i** and **3j**exhibited good efficacy on the DPPH radicals. Similarly **3i** and **3j**exhibited good results in superoxide scavenging method. All the remaining compounds showed moderate antioxidant activities.

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